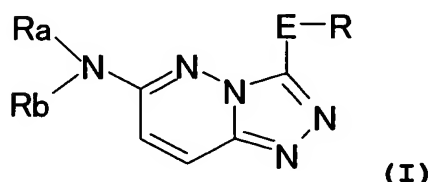


CLAIM

1. A pharmaceutical composition which is a bone mass increasing inducer, comprising a non-living body-derived non-peptide osteoblast differentiation promoting compound as the first component and a bisphosphonate as the second component.

2. The pharmaceutical composition described in claim 1, wherein the first component is a nitrogen-containing heterocyclic compound represented by the following general formula (I) or a salt thereof



(symbols in the formula have the following meanings,

Ra and Rb: the same or different and each represent H; CO-lower alkyl; SO₂-lower alkyl; an optionally substituted cycloalkyl; an optionally substituted aryl; or a lower alkyl which may have 1 to 3 substituents selected from the group consisting of an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted 4- to 8-membered monocyclic saturated or partially unsaturated heterocyclic ring, CO-lower alkyl, SO₂-lower alkyl, OR¹, SR¹, NR¹R², a halogen, NO₂, CN and

COOR¹; provided that at least one of Ra and Rb represents a group other than H; or,

Ra and Rb taken together with an adjacent N atom form a 4- to 8-membered saturated or partially unsaturated heterocyclic ring containing 1 or 2 N atoms as heteroatoms, said heterocyclic ring may be fused with a benzene ring or a cycloalkyl ring and may have a bridge and may form a spiro ring, and said heterocyclic ring may have from 1 to 5 substituent groups,

E: a single bond, a C₁₋₃ alkylene, vinylene (-C=C-), ethynylene (-C≡C-), CO, NR³, CH₂-J, CONR⁴ or NR⁵CO,

J: O, S, NR⁶, CO, SO or SO₂,

R: an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl or an optionally substituted 4- to 8-membered monocyclic saturated or partially saturated heterocyclic ring,

R¹ to R⁶: the same or different and each denotes H or a lower alkyl;

with the proviso that the following compounds are excluded:

(1) a compound wherein Ra and Rb taken together with an adjacent N atom form a piperidino, E is a single bond and R is a piperidino, unsubstituted phenyl, p-

(trifluoromethyl)phenyl, p-chlorophenyl or o-nitrophenyl,

(2) a compound wherein Ra and Rb taken together with an adjacent N atom form a 4-methyl-1-piperazinyl, E is a single bond, and R is an unsubstituted phenyl, p-methylphenyl, m-methylphenyl, p-methoxyphenyl, m-chlorophenyl, p-chlorophenyl or m-nitrophenyl,

(3) a compound wherein R is an optionally substituted imidazolyl, 5-nitro-2-furyl or 5-nitro-2-thienyl,

(4) a compound wherein Ra is H, Rb is cyclopropyl, E is a single bond and R is a p-(trifluoromethyl)phenyl, and

(5) a compound wherein Ra is a methyl, Rb is a 2-hydroxypropyl, E is a single bond and R is a 3-pyridyl).

3. The pharmaceutical composition described in claim 2, wherein the first component is a nitrogen-containing heterocyclic compound selected from 6-Azocan-1-yl-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-azepan-1-yl-3-(6-bromopyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 3-(3-methoxyphenyl)-6-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine, 3-(3-bromophenyl)-6-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-azepan-1-yl-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(4-fluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(3-azabicyclo[3.2.1]octan-3-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(4,4-difluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-

(3,3-difluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-
1,2,4-triazolo[4,3-b]pyridazine, 6-azocan-1-yl-3-(6-
bromopyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, and 6-
(8-azabicyclo[3.2.1]octan-8-yl)-3-(6-bromopyridin-2-yl)-
5 1,2,4-triazolo[4,3-b]pyridazine, or a salt thereof.

4. The pharmaceutical composition described in claim
2, wherein the second component is a bisphosphonate
selected from alendronate, risedronate, pamidronate,
10 incadronate, minodronate, ibandronate and zoledronate.

5. The pharmaceutical composition described in any
one of claims 1 to 4, wherein the bone mass increasing
inducer is a preventive or therapeutic agent for a
15 metabolic bone disease.

6. The pharmaceutical composition described in any
one of claims 1 to 4, wherein the bone mass increasing
inducer is a preventive or therapeutic agent for a bone
20 metabolism turnover reducing type (type II) osteoporosis.

7. A combination product which is a bone mass
increasing inducer consisting of two pharmaceutical
preparations of a pharmaceutical preparation containing a
25 non-living body-derived non-peptide osteoblast
differentiation promoting compound as the first

pharmaceutical preparation and a bisphosphonate as the second pharmaceutical preparation, wherein said first and second pharmaceutical preparations are administered simultaneously or separately.

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8. The combination product described in claim 7, wherein the first pharmaceutical preparation is a pharmaceutical preparation comprising a nitrogen-containing heterocyclic compound represented by the general formula

10 (I) of claim 2, or a salt thereof.

9. The combination product described in claim 7 or 8, which is a kit comprising at least two pharmaceutical preparations of a pharmaceutical preparation containing a non-living body-derived non-peptide osteoblast differentiation promoting compound as the first pharmaceutical preparation and a bisphosphonate as the second pharmaceutical preparation.

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10. An agent for reinforcing the bone mass increasing effect of a non-living body-derived non-peptide osteoblast differentiation promoting compound, which comprises a bisphosphonate as the active ingredient.

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11. The agent described in claim 10, which is an agent for reinforcing the bone mass increasing effect of a

nitrogen-containing heterocyclic compound represented by the general formula (I) of claim 2, or a salt thereof.

12. An agent for reinforcing the bone mass increasing effect of a bisphosphonate, which comprises a non-living body-derived non-peptide osteoblast differentiation promoting compound as the active ingredient.

13. The agent described in claim 12, which is an agent for reinforcing the bone mass increasing effect of a bisphosphonate, wherein it uses a nitrogen-containing heterocyclic compound represented by the general formula (I) of claim 2, or a salt thereof, as the active ingredient.

14. Use of a non-living body-derived non-peptide osteoblast differentiation promoting compound and a bisphosphonate for producing a drug which is a bone mass increasing inducer.

15. Use of a non-living body-derived non-peptide osteoblast differentiation promoting compound for producing a drug which induces increase of bone mass by the concomitant use of a bisphosphonate.

16. Use of a bisphosphonate for producing a drug which reinforces bone mass increasing effect of a non-living body-derived non-peptide osteoblast differentiation promoting compound.

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17. A method for preventing or treating a metabolic bone disease which accompanies reduction of the bone mass and/or bone strength of the patient, which comprises administering an effective amount of a non-living body-derived non-peptide osteoblast differentiation promoting compound and an effective amount of a bisphosphonate, simultaneously or separately.

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18. The method described in claim 17, wherein the metabolic bone disease which accompanies reduction of the bone mass and/or bone strength of the patient is a bone metabolism turnover reducing type (type II) osteoporosis.

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19. A method for inducing bone mass gain of a patient, which comprises administering an effective amount of a non-living body-derived non-peptide osteoblast differentiation promoting compound and an effective amount of a bisphosphonate, simultaneously or separately, to a patient who requires increase of the bone mass and/or bone strength.

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20. The method described in any one of claims 17 to 19, wherein the non-living body-derived non-peptide osteoblast differentiation promoting compound is a nitrogen-containing heterocyclic compound represented by the general formula (I) of claim 2, or a salt thereof.